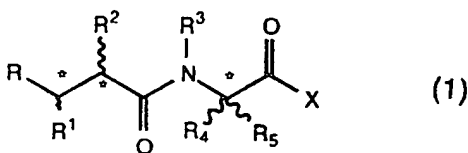




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(54) Title: SULPHAMIDE DERIVATIVES AS METALLOPROTEINASE INHIBITORS

**(57) Abstract**

Compounds of formula (1) are described wherein R represents a -CONHOH, carboxyl (-CO₂H), esterified carboxyl or -P(O)(X¹R⁸)X²R⁹ group, where X¹ and X², which may be the same or different is each an oxygen or a sulphur atom, and R⁸ and R⁹, which may be the same or different each represents a hydrogen atom or an optionally substituted alkyl, aryl or aralkyl group; R¹ represents a hydrogen atom or an optionally substituted alkyl, alkenyl, aryl, aralkyl, heteroaralkyl or heteroaralkylthioalkyl group; R² represents an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkoxy, or aralkylthio group, or an amino (-NH₂), substituted amino, carboxyl (-CO₂H) or esterified carboxyl group; R³ represents a hydrogen atom or an alkyl group; R⁴ represents a hydrogen atom or an alkyl group; R⁵ represents an optionally substituted alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms of -N(R⁷)- groups, [where R⁷ is a hydrogen atom or a C₁₋₆ alkyl group] or a group -(Alk)_nR⁶ where Alk is an alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R⁷)- groups, n is zero or an integer 1, and R⁶ is an optionally substituted cycloalkyl or cycloalkenyl group; X represents a group -NR¹⁰R¹¹ where R¹⁰ is a hydrogen atom or an optionally substituted alkyl, alkanoyl, aryl, aroyl, aralkyl or aralkanoyl group, and R¹¹ is a straight or branched alkylaminosulphonylamino group wherein the alkyl portion is optionally interrupted by one or more -O- or -S- atoms or N(R⁷)- or aminocarbonyloxy groups; and the salts, solvates and hydrates thereof. The compounds are metalloproteinase inhibitors and in particular have a selective inhibitory action against gelatinase and may be of use in the treatment of cancer to control the development of tumour metastases.

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SULPHAMIDE DERIVATIVES AS METALLOPROTEINASE INHIBITORS

Field of the Invention

This invention relates to a novel class of peptidyl derivatives, to processes for their preparation and to their use in medicine.

Background to the Invention

In normal tissues, cellular connective tissue synthesis is offset by extracellular matrix degradation, the two opposing effects existing in dynamic equilibrium. Degradation of the matrix is brought about by the action of proteinases released from resident connective tissue cells and invading inflammatory cells, and is due, in part, to the activity of at least three groups of metalloproteinases. These are the collagenases, the gelatinases (or type-IV collagenases) and the stromelysins. Normally these catabolic enzymes are tightly regulated at the level of their synthesis and secretion and also at the level of their extracellular activity, the latter through the action of specific inhibitors, such as α_2 -macroglobulins and TIMP (tissue inhibitor of metalloproteinase), which form inactive complexes with metalloproteinases.

The accelerated, uncontrolled breakdown of connective tissues by metalloproteinase catalysed resorption of the extracellular matrix is a feature of many pathological conditions, such as rheumatoid arthritis, corneal, epidermal or gastric ulceration; tumour metastasis or invasion; periodontal disease and bone disease. It can be expected that the pathogenesis of such diseases is likely to be modified in a beneficial manner by the administration of metalloproteinase inhibitors and numerous compounds have been suggested for this purpose [for a general review see Wahl, R.C. *et al* Ann. Rep. Med. Chem. 25, 175-184, Academic Press Inc., San Diego (1990)].

Certain hydroxamic acid peptidyl derivatives [see for example European

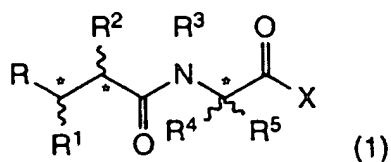
Patent Specifications Nos. 214639, 231081, 236872 and 274453 and International Patent Specifications Nos. WO90/05716 and WO90/05719], have been described as collagenase and/or stromelysin inhibitors.

Summary of the Invention

We have now found a new class of peptidyl derivatives, members of which are metalloproteinase inhibitors and which, in particular, advantageously possess a potent and selective inhibitory action against gelatinase.

There is now much evidence that metalloproteinases are important in tumour invasion and metastasis. Tumour cell gelatinase, in particular, has been associated with the potential of tumour cells to invade and metastasise. Tumour invasion and metastasis is the major cause of treatment failure for cancer patients, and the use of a selective gelatinase inhibitor such as a compound of the present invention which is capable of inhibiting tumour cell invasion can be expected to improve the treatment of this disease.

Thus according to one aspect of the invention we provide a compound of formula (1)



wherein R represents a -CONHOH, carboxyl (-CO₂H), esterified carboxyl or -P(O)(X¹R⁸)X²R⁹ group, where X¹ and X², which may be the same or different is each an oxygen or a sulphur atom, and R⁸ and R⁹, which may be the same or different each represents a hydrogen atom or an optionally substituted alkyl, aryl, or aralkyl group.

R¹ represents a hydrogen atom or an optionally substituted alkyl, alkenyl, aryl, aralkyl, heteroaralkyl or heteroarylthioalkyl group;

R^2 represents an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkoxy, or aralkylthio group, or an amino ($-NH_2$), substituted amino, carboxyl ($-CO_2H$) or esterified carboxyl group;

R^3 represents a hydrogen atom or an alkyl group;

R^4 represents a hydrogen atom or an alkyl group;

R^5 represents an optionally substituted alkyl or alkenyl group optionally interrupted by one or more $-O-$ or $-S-$ atoms or $-N(R^7)-$ groups, [where R^7 is a hydrogen atom or a C_{1-6} alkyl group] or a group $-[Alk]_nR^6$ where Alk is an alkyl or alkenyl group optionally interrupted by one or more $-O-$ or $-S-$ atoms or $-N(R^7)-$ groups, n is zero or an integer 1, and R^6 is an optionally substituted cycloalkyl or cycloalkenyl group;

X represents a group $-NR^{10}R^{11}$ where R^{10} is a hydrogen atom or an optionally substituted alkyl, alkanoyl, aryl, aroyl, aralkyl or aralkanoyl group, and R^{11} is a straight or branched alkylaminosulphonylamino group wherein the alkyl portion is optionally interrupted by one or more $-O-$ or $-S-$ atoms or $-N(R^7)-$ or aminocarbonyloxy groups;

and the salts, solvates and hydrates thereof.

It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms, for example those marked with an asterisk in formula (1). The presence of one or more of these asymmetric centres in a compound of formula (1) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereoisomers, and mixtures, including racemic mixtures, thereof.

In the formulae herein, the \sim -line is used at a potential asymmetric centre to represent the possibility of R - and S - configurations, the \equiv line and the ----- line to represent a unique configuration at an asymmetric centre.

In the compounds according to the invention, when the group R represents an esterified carboxyl group, it may be for example a group of formula

-CO₂R¹⁸ where R¹⁸ is a straight or branched, optionally substituted C₁₋₈alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C₆₋₁₂arylC₁₋₈alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C₆₋₁₂aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆₋₁₂aryloxyC₁₋₈alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl or 2-naphthyloxymethyl group; an optionally substituted C₁₋₈alkanoyloxyC₁₋₈alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C₆₋₁₂aroyloxyC₁₋₈alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the groups R¹⁸ include for example one or more halogen atoms such as fluorine, chlorine, bromine or iodine atoms, or C₁₋₄alkyl, e.g. methyl or ethyl, or C₁₋₄alkoxy, e.g. methoxy or ethoxy, groups.

In general, when the group R represents an esterified carboxyl group, it may be a metabolically labile ester of a carboxylic acid.

When the groups R¹ and/or R² in compounds of formula (1) each represents an optionally substituted alkyl or alkenyl group, it may be, for example, a straight or branched C₁₋₆alkyl or C₂₋₆alkenyl group, such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, ethenyl, 1-propenyl, 1-butenyl or 2-butenyl group optionally substituted by one or more C₁₋₆alkoxy, e.g. methoxy, ethoxy, propoxy, C₁₋₆alkylthio, e.g. methylthio, ethylthio, propylthio, C₆₋₁₂arylC₁₋₆alkoxy, e.g. phenylC₁₋₆alkoxy such as benzyloxy, aralkylthio, e.g. phenylC₁₋₆alkylthio such as benzylthio, amino (-NH₂), substituted amino, [such as -NHR¹⁹, where R¹⁹ is a C₁₋₆alkyl e.g. methyl or ethyl, C₆₋₁₂arylC₁₋₆alkyl, e.g. phenylC₁₋₆alkyl, such as benzyl, C₆₋₁₂aryl, e.g. phenyl, C₃₋₈cycloalkyl, e.g. cyclohexyl, or C₃₋₈cycloalkylC₁₋₆alkyl, e.g. cyclohexylmethyl group], carboxyl (-CO₂H) or -CO₂R¹⁸ [where R¹⁸ is as defined above] groups.

Aryl groups represented by R¹ and/or R² in compounds of formula (1) include C₆₋₁₂aryl groups such as phenyl or 1- or 2-naphthyl groups.

Aralkyl groups represented by R¹ and/or R² include C₆₋₁₂arylC₁₋₆alkyl

groups such as phenylC₁₋₆alkyl, or 1- or 2-naphthylC₁₋₆alkyl, for example benzyl, phenylethyl, phenylpropyl, phenylbutyl, phenylpentyl, 1- or 2-naphthylmethyl, naphthylethyl, naphthylpropyl, naphthylbutyl or naphthylpentyl groups.

When the group R¹ in compounds of formula (1) is a heteroaralkyl group, it may be for example a C₃₋₆heteroarylC₁₋₆alkyl group, such as an optionally substituted pyrrolylmethyl, furanylmethyl, thienylmethyl, imidazolymethyl, oxazolymethyl, thiazolymethyl, pyrazolymethyl, pyridinylmethyl or pyrimidinylmethyl group.

Heteroarylthioalkyl groups represented by R¹ include C₃₋₆heteroarylthioC₁₋₆alkyl groups such as optionally substituted pyrrolylthiomethyl, furanylthiomethyl, oxazolylthiomethyl, thiazolylthiomethyl, pyrazolylthiomethyl, pyridinylthiomethyl or pyrimidinylthiomethyl groups.

Optional substituents which may be present on heteroaralkyl or heteroarylthioalkyl groups represented by R¹ include those discussed below in relation to R¹ and/or R² when these groups are for example aralkyl or aralkylthioalkyl groups.

Cycloalkyl groups represented by the group R² in compounds according to the invention include C₃₋₈cycloalkyl groups such as cyclopentyl or cyclohexyl groups.

When R² is a cycloalkylalkyl group it may be for example a C₃₋₈cycloalkylC₁₋₆alkyl group such as a cyclopentylC₁₋₆alkyl or cyclohexylC₁₋₆alkyl group, for example a cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclopentylbutyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, or cyclohexylbutyl group.

When R² is an aralkoxy or an aralkylthio group it may be for example a C₆₋₁₂arylC₁₋₆alkoxy or C₆₋₁₂arylC₁₋₆alkylthio group such as a phenylC₁₋₆alkoxy or phenylC₁₋₆alkylthio group, e.g. a benzyloxy, phenylethoxy, phenylpropoxy, phenylbutoxy, benzylthio, phenylethylthio, phenylpropylthio or phenylbutylthio group.

The cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkoxy or aralkylthio groups represented by R^1 and/or R^2 in compounds of formula (1) may each optionally be substituted in the cyclic part of the group by one, two or more substituents [R^{16}] selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6} alkyl, e.g. methyl or ethyl, C_{1-6} alkoxy e.g. methoxy or ethoxy, C_{2-6} alkylenedioxy, e.g. ethylenedioxy, halo C_{1-6} alkyl, e.g. tri-fluoromethyl, C_{1-6} alkylamino, e.g. methylamino or ethylamino, C_{1-6} dialkylamino, e.g. dimethylamino or diethylamino, amino ($-NH_2$), nitro, cyano, hydroxyl ($-OH$), carboxyl ($-CO_2H$), $-CO_2R^{18}$, where R^{18} is as defined above, C_{1-6} alkylcarbonyl, e.g. acetyl, sulphonyl ($-SO_3H$), C_{1-6} alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6} alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6} dialkylaminosulphonyl e.g. dimethylaminosulphonyl or diethylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6} alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6} dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, sulphonylamino ($-NH-SO_2H$), C_{1-6} alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, or C_{1-6} dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino groups. It will be appreciated that where two or more R^{10} substituents are present, these need not necessarily be the same atoms and/or groups. The R^{16} substituents may be present at any ring carbon atom away from that attached to the rest of the molecule of formula (1). Thus, for example, in phenyl groups any substituents may be present at the 2-, 3- or 4- 5- or 6- positions relative to the ring carbon atom attached to the remainder of the molecule.

When the group R^2 in compounds of formula (1) is a substituted amino group, this may be for example a group $-NHR^{19}$ where R^{19} is as defined above.

Esterified carboxyl groups represented by R^2 include groups of formula $-CO_2R^8$ where R^8 is as defined above.

When the groups R^3 and R^4 in compounds of formula (1) are alkyl groups, they may be for example C_{1-6} alkyl groups such as methyl or ethyl groups.

The group R^5 in compounds of formula (1) may be an optionally substituted

straight or branched C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl or n-hexyl or C₂₋₆alkenyl e.g. ethenyl or 1-propenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R⁷)- groups where R⁷ is a hydrogen atom or a C₁₋₆alkyl group such as a methyl group.

Optional substituents which may be present on alkyl or alkenyl groups R⁵ include C₆₋₁₂arylC₁₋₆alkyl groups such as optionally substituted phenylC₁₋₆alkyl e.g. benzyl groups, C₆₋₁₂arylC₁₋₆alkoxy groups such as optionally substituted phenylC₁₋₆alkoxy e.g. benzyloxy groups, C₆₋₁₂aryl e.g. optionally substituted phenyl groups, C₃₋₈heteroaryl e.g. optionally substituted indole, imidazole or quinoline groups, C₆₋₁₂arylC₁₋₆alkoxyC₆₋₁₂aryl, e.g. benzyloxyphenyl groups, -OH, -SH, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxy (-CO₂H), amino (-NH₂), carboxamido (-CONH₂) or guanido -NHC(NH₂)=NH, groups. The optional substituents present on these groups may be R¹⁰ substituents as discussed above.

When the group Alk is present in compounds of formula (1) it may be a straight or branched C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl i-propyl, n-butyl, i-butyl, n-pentyl or n-hexyl or C₂₋₆alkenyl e.g. ethenyl or 1-propenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R⁷)- groups where R⁷ is a hydrogen atom or a C₁₋₆alkyl group such as a methyl group.

The group R⁶ in compounds of formula (1) may represent a C₃₋₈cycloalkyl, e.g. cyclopentyl or cyclohexyl, or C₃₋₈cycloalkenyl e.g. cyclopentenyl or cyclohexenyl, group optionally substituted by one, two or more C₁₋₆alkyl, e.g. methyl or ethyl, C₁₋₆alkoxy, e.g. methoxy or ethoxy, C₁₋₆alkylthio, e.g. methylthio, or hydroxyl groups.

The group X in compounds of formula (1) may be a group -NR¹⁰R¹¹ where R¹⁰ is a hydrogen atom or an optionally substituted C₁₋₆alkyl, e.g. methyl or ethyl, C₂₋₄alkanoyl, e.g. acetyl or propionyl, C₆₋₁₂arC₁₋₃alkyl, e.g. phenC₁₋₃alkyl such as benzyl or phenethyl, C₆₋₁₂ aryl e.g. phenyl, C₆₋₁₂ aroyl, e.g. benzoyl, or C₆₋₁₂arC₁₋₃alkanoyl, e.g. phenC₁₋₃alkanoyl such as a methylphenylketone group and R¹¹ is a straight or branched C₁₋₆alkylaminosulphonylamino group wherein the alkyl portion is optionally interrupted by one or more -O- or -S- atoms or -N(R⁷)- or aminocarbonyloxy groups. Thus for example R¹¹ may be a group Alk¹N(R⁷)SO₂NR¹²R¹³

where Alk^1 is a C_{1-6} alkyl group as just defined and wherein R^{12} and R^{13} which may be the same or different is each a hydrogen atom or an optionally substituted straight or branched alkyl group optionally interrupted by one or more -O- or -S- atoms or -N(R^7)- or aminocarbonyloxy groups; or R^{12} and R^{13} , together with the nitrogen atom to which they are attached, may form an optionally substituted C_{3-6} cyclic amino group optionally possessing one or more other heteroatoms, selected from -O- or -S-, or -N(R^7)- groups.

The alkyl portion, Alk^1 of the alkylaminosulphonylamino group represented by R^{11} may in particular be a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group optionally interrupted by one or more -O- or -S- atoms or -N(R^7) or aminocarbonyloxy groups and may be for example a methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, or ethylaminocarbonyloxymethyl group.

When R^{12} and/or R^{13} is an alkyl group it may be for example a C_{1-6} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl group, optionally interrupted by one or more -O- or -S- atoms, or -N(R^7)- or aminocarbonyloxy groups and may be for example a methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl or ethylaminocarbonyloxymethyl group. The optional substituents which may be present on such groups include hydroxyl (-OH), carboxyl ($-\text{CO}_2\text{H}$), esterified carboxyl ($-\text{CO}_2\text{R}^{18}$), carboxamido ($-\text{CONH}_2$), substituted carboxamido, e.g. a group $-\text{CONR}^{12}\text{R}^{13}$ where $\text{NR}^{12}\text{R}^{13}$ is as defined herein, amino ($-\text{NH}_2$), substituted amino, for example a group of formula $-\text{NR}^{12}\text{R}^{13}$, or aryl, e.g. C_{6-12} aryl such as phenyl, optionally substituted by one, two or more R^{10} substituents selected from those listed above in relation to the group R^2 .

Particular examples of cyclic amino groups represented by $-\text{NR}^{12}\text{R}^{13}$ include morpholinyl, imidazolyl, piperazinyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, pyrrolidinyl, pyridinyl and pyrimidinyl groups.

The groups R^8 or R^9 in compounds of formula (1) may be hydrogen atom or an optionally substituted straight or branched C_{1-6} alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or i-butyl, C_{6-12} aryl e.g. phenyl, or C_{6-12} aryl C_{1-}

C_6 alkyl, e.g. benzyl, phenylethyl or phenylpropyl group. Optional substituents present on alkyl groups of this type include one or more C_{1-6} alkoxy, e.g. methoxy, ethoxy, or C_{1-6} alkylthio e.g. methylthio or ethylthio groups or an optionally substituted C_{6-12} aryloxy, e.g. phenyloxy, C_{6-12} arylthio e.g. phenylthio, C_{6-12} aryl C_{1-6} alkoxy e.g. benzyloxy or C_{6-12} aryl C_{1-6} alkylthio e.g. benzylthio. Optional substituents present on the group R^8 or R^9 when it is an aryl or aralkyl group or an alkyl group substituted by an aryloxy or arylthio group include R^{10} groups present on the cyclic part of R^8 or R^9 as defined above.

Salts of compounds of formula (1) include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as hydrochlorides, hydrobromides, hydroiodides, p-toluene sulphonates, phosphates, sulphates, acetates, trifluoroacetates propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartarates and benzoates.

Salts may also be formed with bases. Such salts include salts derived from inorganic or organic bases, for example alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

When the group R in compounds of the invention is an esterified carboxyl group, it may be a metabolically labile ester of formula $-CO_2R^{18}$ where R^{18} may be an ethyl, benzyl, phenylethyl, phenylpropyl, 1- or 2-naphthyl, 2,4-dimethylphenyl, 4-t-butylphenyl, 2,2,2-trifluoroethyl, 1-(benzyloxy)benzyl, 1-(benzyloxy)ethyl, 2-methyl-1-propionyloxypropyl, 2,4,6-trimethylbenzoyloxymethyl or pivaloyloxymethyl group.

When the group R in compounds of formula (1) is a $-P(O)(X^1R^8)X^2R^9$ group it may in particular be a $-P(O)(OH)OR^9$, $-P(O)(SH)OR^9$ or $-P(O)(OH)SR^9$ group. Examples of such groups include $-P(O)(OH)OH$, $-P(O)(OH)SH$, $-P(O)(SH)OH$, $-P(O)(OH)OCH_3$, $-P(O)(OH)SCH_3$, $-P(O)(OH)OCH_2CH_3$, $-P(O)(OH)OPh$, $-P(O)(OH)SPh$, $-P(O)(OH)OCH_2Ph$ or $-P(O)(OH)SCH_2Ph$, where Ph is a phenyl group optionally substituted by one or more substituents R^{10} .

In the compounds of formula (1) the group R¹ may in particular be a C₁₋₆alkyl group such as a methyl group, an aralkyl group such as benzyl group, an arylthioalkyl group such as a phenylthiomethyl group or a heteroarylthioalkyl group such as thienylthiomethyl, pyridinylthiomethyl or pyrimidinylthiomethyl group or is especially a hydrogen atom.

The group R² may be in particular an optionally substituted C₁₋₆alkyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkylC₁₋₆alkyl, C₆₋₁₂aryl, C₆₋₁₂arylC₁₋₆alkoxy or C₆₋₁₂aralkylthio group and, especially, a C₆₋₁₂arylC₁₋₆alkyl group. Particular types of these groups are optionally substituted C₃₋₆alkyl, such as n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl or i-pentyl; cyclopentyl; cyclohexyl; cyclopentylC₁₋₆alkyl, such as cyclopentylC₃₋₆alkyl, e.g. cyclopentylpropyl, cyclopentylbutyl, or cyclopentylpentyl; phenyl; 1- or 2-naphthyl; phenylC₁₋₆alkoxy, e.g. phenylethoxy, phenylpropoxy or phenylbutoxy; phenylC₁₋₆alkylthio, e.g. phenylethylthio, phenylpropylthio or phenylbutylthio; and, especially, phenylC₁₋₆alkyl such as phenylC₃₋₆alkyl e.g. phenylpropyl, phenylbutyl or phenylpentyl; or 1- or 2-naphthylC₁₋₆alkyl such as 1- or 2-naphthylC₃₋₆alkyl, e.g. 1- or 2-naphthylpropyl, naphthylbutyl or naphthylpentyl. Each of these cycloalkyl or aryl groups may be substituted, by one two or more substituents R¹⁶ described above.

The groups R³ and R⁴ in compounds of formula (1) may each in particular be a methyl group, or, especially, a hydrogen atom.

The group R⁵ in compounds of formula (1) may be in particular a group -AlkR⁶, where R⁶ is an optionally substituted cycloalkyl or cycloalkenyl group.

Thus, the group R⁵ in compounds of formula (1) may be an optionally substituted C₃₋₈cycloalkylC₁₋₆alkyl [e.g. cyclopentylC₁₋₆alkyl such as cyclopentylmethyl or cyclopentylethyl, or cyclohexylC₁₋₆alkyl such as cyclohexylmethyl or cyclohexylethyl], C₃₋₈cycloalkenylC₁₋₆alkyl [e.g. cyclopentenylC₁₋₆alkyl such as cyclopentenylmethyl or cyclohexenylC₁₋₆alkyl such as cyclohexenylmethyl], cycloalkylC₁₋₃alkoxyC₁₋₃alkyl [e.g. cyclopentylmethoxymethyl, cyclohexylmethoxymethyl] C₃₋₈cycloalkenylC₁₋₃alkoxyC₁₋₃alkyl [e.g. cyclopentenylmethoxymethyl or

cyclohexenylmethoxymethyl] C₃₋₈cycloalkylC₁₋₃alkylthioC₁₋₃alkyl [e.g. cyclopentylmethylthiomethyl or cyclohexylmethylthiomethyl] or C₃₋₈cycloalkenylC₁₋₃alkylthioC₁₋₃alkyl [e.g. cyclopentenylmethylthiomethyl or cyclohexenylmethylthiomethyl], C₃₋₈cycloalkylC₁₋₃alkylaminoC₁₋₃alkyl [e.g. cyclopentylmethylaminomethyl, or cyclohexylmethylaminomethyl] or C₃₋₈cycloalkenylC₁₋₃alkylaminoC₁₋₃alkyl [e.g. cyclopentenylmethylaminomethyl or cyclohexenylmethylaminomethyl] group.

In another preference, the group R⁵ in compounds of formula (1) may in particular be a C₁₋₆alkyl group, e.g. an i-propyl or i-butyl group, or an optionally substituted benzyl, benzyloxybenzyl or indolylmethyl group.

The group X in compounds of formula (1) is preferably a group -NR¹⁰R¹¹ where R¹⁰ is a hydrogen atom or an optionally substituted C₁₋₆alkyl group, such as methyl or ethyl group.

In another preference, the group X is preferably -NR¹⁰R¹¹ where R¹¹ is an Alk¹N(R⁷)SO₂NR¹²R¹³ group, wherein Alk¹ is straight or branched C₁₋₆alkyl optionally interrupted by one or more -O- or -S- atoms or -N(R⁷)- or aminocarbonyloxy groups. Compounds of this type where Alk¹ is a C₁₋₃alkyl group, e.g. a methyl, ethyl or n-propyl group optionally interrupted by one or more -O- or -S- atoms or -N(R⁷)- [e.g. -NH- or -N(CH₃)-] or aminocarbonyloxy groups are especially useful.

The group -N(R⁷)SO₂NR¹²R¹³ in compounds of formula (1) may in particular be a group -NHSO₂NR¹²R¹³ or -N(CH₃)SO₂NR¹²R¹³.

In another group of compounds of formula (1) the group -N(R⁷)SO₂NR¹²R¹³ may be for example a group -N(R⁷)SO₂NH₂, -N(R⁷)SO₂NHR¹³ or -N(R⁷)SO₂NR¹²R¹³ where R¹² and R¹³ is each an optionally substituted C₁₋₆alkyl group or R¹² and R¹³ together with the nitrogen atom to which they are attached is an optionally substituted C₃₋₆cyclic amino group, for example a morpholinyl group.

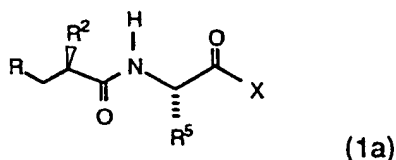
A particularly useful group of compounds according to the invention is that of formula (1) wherein R⁵ is an AlkR⁶ group, where Alk is a C₁₋₆alkyl and R⁶ is a cycloalkyl or cycloalkenyl group.

Another particularly useful group of compounds according to the invention is that of formula (1) where R^2 is an optionally substituted alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkoxy or aralkylthio group.

In general, in compounds of formula (1) the groups R^1 , R^3 and R^4 is each preferably a hydrogen atom.

In a further preference, the group R in compounds according to the invention is a -CONHOH or a -CO₂H group or a metabolically labile ester thereof, or a group P(O)(OH)OR⁷. In a particular preference, however, R is a -CONHOH, -CO₂H or -P(O)(OH)₂ group.

An especially useful group of compounds according to the invention has the formula (1a).



wherein R, R^2 , R^5 and X are as defined for formula (1); and the salts, solvates and hydrates thereof.

A particularly useful group of compounds of formula (1a) are those wherein R represents a -CONHOH, or -CO₂H or -P(O)(OH)₂ group; R^2 represents an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkoxy or aralkylthio group;

R^5 represents a group -AlkR⁶, where Alk is a C₁₋₆ alkyl group and R⁶ is a cycloalkyl or cycloalkenyl group;

X is a group -NR¹⁰R¹¹; and the salts, solvates and hydrates thereof.

Particularly useful compounds of formula (1a) are those wherein R^5 is a group -AlkR⁶, and R⁶ is an optionally substituted cyclohexyl group. Compounds of this type in which R^5 is a cyclohexylC₁₋₆alkyl group,

Other useful compounds of formula (1a) include those wherein R^2 represents a C_{3-6} alkyl group, particularly an i-butyl or n-pentyl group, or a cycloalkyl C_{3-6} alkyl group, particularly a cyclohexylpropyl, cyclohexylbutyl or cyclohexylpentyl group, or especially an optionally substituted phenyl C_{2-6} alkyl group particularly an optionally substituted phenylethyl, phenylpropyl, phenylbutyl or phenylpentyl group. Optional substituents on the phenyl group may be one, two or more R^{16} groups as defined for compounds of formula (1).

In the compounds of formula (1a) X may be a group $-NR^{10}R^{11}$ where R^{11} is $Alk^1N(R^7)SO_2NR^{12}R^{13}$ and R^{10} is a hydrogen atom or a C_{1-6} alkyl group, especially a methyl or ethyl group. Particular compounds of this type are those wherein X is $-NHAik^1N(R^7)SO_2NR^{12}R^{13}$.

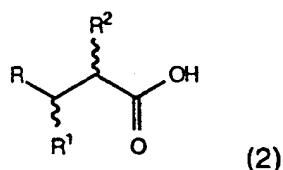
An especially useful group of compounds according to the invention has the formula (1a) wherein R^2 is an optionally substituted phenyl C_{3-6} alkyl group, especially an optionally substituted phenylbutyl or in particular a phenylpropyl group; R^5 is a cyclohexylmethyl group; and X is a group $-NR^{10}R^{11}$, especially a group $-NHAik^1N(R^7)SO_2NR^{12}R^{13}$.

In the compounds of formulae (1) and (1a), when the group R^5 is a cycloalkyl C_{1-6} alkyl group then the chiral centre to which this group is attached preferably has a S-configuration.

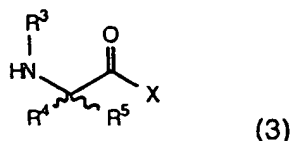
The compounds according to the invention may be prepared by the following processes. In the description and formulae below the groups R, R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined above, except where otherwise indicated. It will be appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable amino or hydroxyl protecting groups include benzyl, benzyloxycarbonyl or t-butyloxycarbonyl groups. These may be removed from a protected derivative by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as

presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an alcohol e.g. methanol, or by treatment with trimethylsilyl iodide or trifluoroacetic acid in an aqueous solvent. Suitable carboxyl protecting groups include benzyl groups, which may be removed from a protected derivative by the methods just discussed, or alkyl groups, such as a t-butyl group which may be removed from a protected derivative by treatment with trifluoroacetic acid in an aqueous solvent. Other suitable protecting groups and methods for their use will be readily apparent. The formation of the protected amino, hydroxyl or carboxyl group may be achieved using standard alkylation or esterification procedures, for example as described below.

Thus according to a further aspect of the invention a compound of formula (1) may be prepared by coupling an acid of formula (2)



or an active derivative thereof, with an amine of formula (3)



followed by removal of any protecting groups.

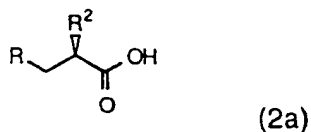
Active derivatives of acids for formula (2) include for example acid anhydrides, or acid halides, such as acid chlorides.

The coupling reaction may be performed using standard conditions for amination reactions of this type. Thus, for example the reaction may be achieved in a solvent, for example an inert organic solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, an amide e.g. a substituted amide such as dimethylformamide, or a halogenated hydrocarbon such as dichloromethane at a low temperature, e.g. -30°C to

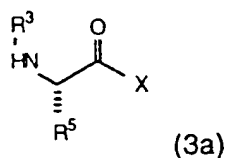
ambient temperature, such as -20°C to 0°C, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine or a cyclic amine such as N-methylmorpholine. Where an acid of formula (2) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a triazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate for example ethylchloroformate, prior to reaction with the amine of formula (3).

Free hydroxyl or carboxyl groups in the starting materials of formulae (2) and (3) may need to be protected during the coupling reaction. Suitable protecting groups and methods for their removal may be those mentioned above. Where R in the intermediates of formula (2) is a -P(O)(X¹R⁸)X²R⁹ group, at least one of R⁸ or R⁹ is other than a hydrogen atom. Conveniently, each of R⁸ and R⁹ is a optionally substituted alkyl, aryl or aralkyl group. Such groups, when present in compounds of the invention may be cleaved as described below to yield other compounds of the invention wherein R⁸ and/or R⁹ is each a hydrogen atom.

It will be appreciated that where a particular stereoisomer of formula (1) is required, this may be obtained by resolution of a mixture of isomers following the coupling reaction of an acid of formula (2) and an amine of formula (3). Conventional resolution techniques may be used, for example separation of isomers by Chromatography e.g. by use of high performance liquid chromatography. Where desired, however, appropriate homochiral starting materials may be used in the coupling reaction to yield a particular stereo isomer of formula (1). Thus, in a particular process a compound of formula (1a) may be prepared by reaction of a compound of formula (2a)

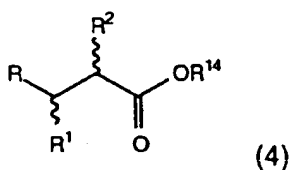


with an amine of formula (3a)



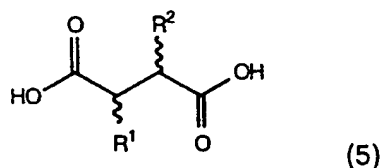
as described above

Intermediate acids of formula (2) wherein R is a carboxyl or esterified carboxyl group or a group $-P(O)(X^1R^8)X^2R^9$ may be prepared from a corresponding ester of formula (4)



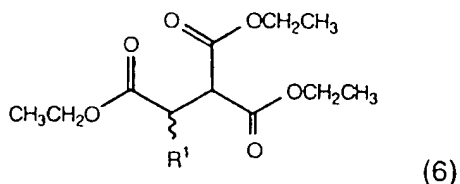
where R^{14} is an alkyl group, for example a methyl or t-butyl group, by hydrolysis using for example trifluoroacetic acid, or, when R^{14} is an aralkyl group, such as a benzyl group, by hydrogenolysis, for example by reaction with hydrogen in the presence of a metal catalyst, e.g. palladium, on a support such as carbon in a solvent such as an alcohol, e.g. methanol optionally at an elevated pressure and temperature.

An ester of formula (4) where R is a carboxyl or esterified carboxyl group may be prepared by esterification of the corresponding acid of formula (5)



using an appropriate acyl halide, for example an acyl chloride in a solvent such as an alcohol, e.g. methanol at a low temperature, e.g. around 0°C .

Acids of formula (5) may be prepared by alkylation of a compound of formula (6)



with an appropriate halide, e.g. a compound $R^2\text{Hal}$, where Hal is a halogen atom such as a chlorine or bromine atom in the presence of a base, for example an alkoxide such as sodium ethoxide in a solvent such as an alcohol, e.g. ethanol at ambient temperature, followed by decarboxylation using for example concentrated hydrochloric acid at an elevated temperature, e.g. the reflux temperature.

Intermediates of formula (6) are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

Intermediate esters of formula (4) where R is a $-\text{P}(\text{O})(\text{X}^1\text{R}^8)\text{X}^2\text{R}^9$ group may be prepared by reaction of an acrylate $\text{R}^1\text{CHC}(\text{R}^2)\text{COR}^{14}$ with a phosphite $-\text{P}(\text{OR}^{15})(\text{X}^1\text{R}^8)\text{X}^2\text{R}^9$ [where R^{15} is a leaving group, for example a silyl group such as a trialkylsilyl group e.g. a trimethylsilyl group] at an elevated temperature.

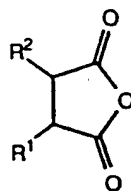
Acrylates of formula $\text{R}^1\text{CHC}(\text{R}^2)\text{COOR}^{14}$ may be prepared by reaction of a mono-ester $\text{HOOCCH}(\text{R}^2)\text{COOR}^{14}$ with an aldehyde R^1CHO or a polymer thereof e.g. paraformaldehyde or paraldehyde in the presence of a base, for example an organic base such as piperidine. The reaction may be performed in a solvent, such as pyridine, optionally at an elevated temperature.

Mono-esters of formula $\text{HOOCCH}(\text{R}^2)\text{COOR}^{14}$ may be prepared by hydrolysis of the corresponding di-ester $\text{R}^{14}\text{OOCCH}(\text{R}^2)\text{COOR}^{14}$ using a base, for example an alkali hydroxide, in an inert solvent such as dioxan at a low temperature e.g. around 0°C . The di-esters for use in this reaction may be prepared by alkylation of the corresponding malonates of formula $\text{R}^{14}\text{OOCCH}_2\text{COOR}^{14}$ with a halide R^2Hal [where Hal is a halogen atom such as a chlorine or bromine atom] in the presence of a base, e.g. a hydride such as sodium hydride in a solvent such as tetrahydrofuran at

ambient temperature. Malonates of formula $R^{14}OOCCH_2COOR^{14}$ are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

Intermediate phosphites of formula $-P(OR^{15})(X^1R^8)X^2R^9$ may be prepared by reaction of a phosphite $-P(O)(X^1R^8)X^2R^9$ with an appropriate amine $(R^{15})_2NH$ e.g. a silazane, at an elevated temperature, e.g. the reflux temperature. Phosphites of formula $P(O)(X^1R^8)X^1R^9$ are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

Intermediate acids of formula (4) wherein R is a $-CONHOH$ group or a protected derivative thereof may be prepared by reaction of an anhydride of formula (7)



(7)

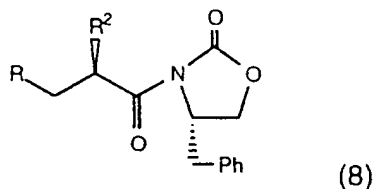
with a hydroxylamine such as O-benzylhydroxylamine in a solvent such as tetrahydrofuran at a low temperature, e.g. around $-20^{\circ}C$, followed where desired by removal of the protecting group as described above.

The intermediate anhydrides of formula (7) may be prepared for example by heating for example at the reflux temperature, a diacid of formula (5) where R is $-CO_2H$ with an acyl chloride such as acetyl chloride.

Intermediate amines of formula (3) may be prepared by reaction of the corresponding acids $R^3NHC(R^4)(R^5)COOH$ or active derivatives thereof with an amine XH using the reagents and conditions described above for the preparation of compounds of formula (1) from intermediates for formula (2) and (3). The acids $R^3NHC(R^4)(R^5)COOH$ and amines XH are either known compounds or may be prepared from known starting materials using analogous processes [for example as described in the preparation of the specific Intermediates in the Examples herein] to those used for the

preparation of the known compounds.

The homochiral acids of formula (2a) may be prepared according to another feature of the invention by oxidation of an oxazolidinone of formula (8)



(where Ph is a phenyl group)

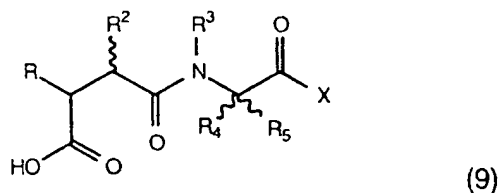
using an oxidising agent such as peroxide, e.g. hydrogen peroxide in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a low temperature, e.g. around 0°C followed by treatment with a base, such as lithium hydroxide, at an elevated temperature.

The compounds of formula (8) are novel, particularly useful, intermediates for the preparation of stereoisomers of formula (1a) and form a further aspect of the invention.

The compounds of formula (8) may be prepared by reaction of an acyl halide $(R^2)COHal$ (where Hal is a halogen atom such as chlorine, bromine or iodine atom) with a solution of (S)-4-(phenylmethyl)-2-oxazolidinone in the presence of a base such as n-butyl lithium in a solvent such as tetrahydrofuran at a low temperature, e.g. around -78°C, followed by treatment of the resulting oxazolidinone with a reagent RCH_2Hal in the presence of a silazide such as sodium hexamethyldisilazide at a low temperature.

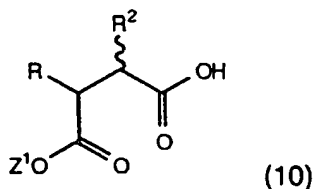
Acyl halides R^2COHal may be prepared by treatment of the corresponding known acids R^2CO_2H with conventional halogenating agents for example thionyl halides under standard reaction conditions.

In another process according to the invention, a compound of formula (1) where R is a carboxyl group may be prepared by decarboxylation of a corresponding compound of formula (9)



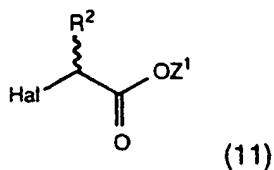
The reaction may be achieved using standard conditions, for example by heating a compound of formula (9) in an inert solvent, such as an aromatic hydrocarbon, e.g. xylene, at the reflux temperature.

The intermediate acids of formula (9) may be prepared by reaction of a protected acid of formula (10)



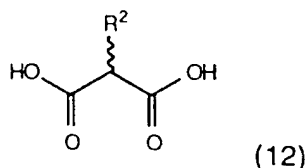
where R is a protected carboxyl group such as a benzyloxycarbonyl group and Z¹ is a protecting group such as a benzyl group with an amine of formula (3) using reagents and conditions as described above for coupling compounds of formula (2) and (3), followed by removal of the protecting groups.

The intermediates of formula (10) may be prepared by treatment of an appropriate malonic ester RCH₂CO₂Z¹ with a halide of formula (11)



(where Hal is a halogen atom, e.g. a chlorine or bromine atom) in the presence of a base such as potassium t-butoxide in a solvent such as dimethylformamide at ambient temperature.

Halides of formula (11) may be prepared by halogenation and subsequent decarboxylation of a di-acid of formula (12).



using for example a halogenating agent such as bromine in a solvent such as diethyl ether at ambient temperature, followed by heating of the resulting halogenated intermediate in a solvent such as an aromatic hydrocarbon e.g. xylene, at the reflux temperature.

Intermediates of formula (12) may be prepared by hydrolysis of the corresponding di-alkylester (e.g. the dimethyl or diethyl ester using a base such as sodium or potassium hydroxide in a solvent such as an alcohol e.g. methanol at the reflux temperature. The di-alkyl ester starting materials are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds, for example as described in the Examples herein.

Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1). Thus, for example, a compound of formula (1) wherein R is a -CONHOH group may be prepared by reaction of a corresponding acid of formula (1) wherein R is a -CO₂H group or an active derivative thereof (for example an acid chloride or an acid anhydride) with hydroxylamine or an O-protected derivative for example O-trimethylsilylhydroxylamine or a salt thereof. The reaction may be performed using the reagents and conditions described above in the preparation of compounds of formula (1) from the starting materials of formulae (2) and (3). If desired the acid starting material may be reacted with a chloroformate, for example ethyl chloroformate, prior to reaction with the hydroxylamine or protected hydroxylamine.

In another interconversion process, compounds of formula (1) wherein R is -CO₂H may be prepared by hydrolysis of the corresponding esterified compounds (for example where R is a -CO₂R¹⁸ group and/or X contains a

similar group) using conventional procedures, for example by treatment with a base, e.g. an alkali metal hydroxide such as lithium hydroxide in a solvent such as an aqueous alcohol, e.g. aqueous methanol, or by treatment with an acid such as a mineral acid, e.g. hydrochloric acid in the presence of a solvent, e.g. dioxan.

Similarly esters of formula (1), for example where R is a CO_2R^{18} group and/or X contains a $-\text{CO}_2\text{R}^{18}$ group may be prepared by reaction of the corresponding acids, where R is a $-\text{CO}_2\text{H}$ group and/or X contains a $-\text{CO}_2\text{H}$ group or an active derivative thereof, with an alcohol R^{18}OH using standard conditions.

The compounds according to the invention are potent and selective inhibitors of gelatinase. The activity and selectivity of the compounds may be determined by the use of appropriate enzyme inhibition test for example as described in Example A hereinafter. In our tests using this approach, compounds according to the invention have been shown to inhibit gelatinase with K_i values in the picomolar-nanomolar range and to have around a 40 fold or greater selectivity for gelatinase over stromelysin, and around a 100-fold or greater selectivity for gelatinase over collagenase.

The ability of compounds of the invention to prevent tumour cell invasion may be demonstrated in a standard mouse model.

Thus, briefly, nude mice may be inoculated with a tumour cell line showing gelatinase - dependent invasion and the ability of compounds according to the invention to reduce subsequent lung tumour colonisation may be evaluated in accordance with standard procedures. In our tests, compounds according to the invention, when administered intravenously at 1mg/kg to mice in the above model have reduced lung tumour colonisation to negligible levels.

The compounds according to the invention can be expected to be of use to prevent tumour cell metastasis and invasion. The compounds may therefore be of use in the treatment of cancer, particularly in conjunction with radiotherapy, chemotherapy or surgery, or in patients presenting with primary tumours, to control the development of tumour metastasis. Thus,

according to a further aspect of the invention we provide a compound of formula (1) for use in the treatment of cancer to control the development of tumour metastasis. Particularly cancers may include breast, melanoma, lung, head, neck or bladder cancers.

For use according to this aspect of the invention, the compounds of formula (1) may be formulated in a conventional manner, optionally with one or more physiologically acceptable carriers, diluents or excipients.

Thus according to a further aspect of the invention we provide a pharmaceutical composition comprising a compound of formula (1) and a pharmaceutically acceptable diluent, carrier or excipient.

In a still further aspect the invention provides a process for the production of a pharmaceutical composition comprising bringing a compound of formula (1) into association with a pharmaceutically acceptable diluent, carrier or excipient.

Compounds for use according to the present invention may be formulated for oral, buccal, parental or rectal administration or in a form suitable for nasal administration or administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles; and preservatives. The preparations may also contain buffer salts, flavouring,

colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (1) may be formulated for parental administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of formula (1) may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispenser device may be accompanied by instructions for administration.

The doses of compounds of formula (1) used to control the development of tumour metastases will vary depending on the condition of the patient to be treated but in general may be in the range around 0.5mg to 100mg/kg body weight, particularly from about 1mg to 40mg/kg body weight. Dosage units may be varied according to the route of administration of the compound and condition of the patient in accordance with conventional practice.

The following Examples illustrate the invention.

Example A

The activity and selectivity of the compounds of the invention may be determined as described below.

All enzyme assays to determine K_i values were performed using the peptide substrate Dnp-Pro-Leu-Gly-Trp-Ala-D-Arg-NH₂. [M. Sharon Stock and Rober D. Gray, JBC 264, 4277-81, 1989). The enzymes cleave at the Gly-Leu bond which can be followed fluorimetrically by measuring the increase in Trp fluorescence emission associated with the removal of the quenching dinitrophenol (Dnp) group.

Essentially, enzyme (e.g. gelatinase, stromelysin, collagenase) at 0.08-2nM; a range of inhibitor concentrations ($0.1-50 \times K_i$) and substrate (approx. 20 μ M) are incubated overnight in 0.1M Tris/HCl buffer, pH 7.5, containing 0.1M NaCl, 10mM CaCl₂ and 0.05% Brij 35 at either room temperature or 37°C depending on the enzyme. The reaction is stopped by adjusting the pH to 4 using 0.1M sodium acetate buffer and the fluorescence read at an excitation wavelength of 280nm and emission wavelength of 346nm.

K_i values can be established using the equation for tight-binding inhibition: -

$$V_i = \frac{V_o}{2[E]} \left(\sqrt{(K_{i(app)} + [I])^2 + 2(K_{i(app)} - [I])[E] + [E]^2} - (K_{i(app)} + [I] - [E]) \right)$$

where V_0 is the initial rate of reaction in the absence of inhibitor, V_i is the initial rate in the presence of inhibitor, $[E]$ is the total enzyme concentration and $[I]$ the total inhibitor concentration in the reaction mixture.

For stromelysin and collagenase, K_i (app) was assumed to approximate to the true K_i as $[S] \ll K_m$ for the substrate hydrolysis. For gelatinase the K_i was determined by performing the analyses at several substrate concentrations. A plot of K_i (app) vs. $[S]$ then gave the true K_i as the value of the y-axis intercept.

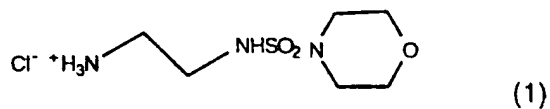
The following results were obtained with compounds according to the invention.

<u>K_i(nM)</u>			
<u>Compound of</u>	<u>Collagenase</u>	<u>Stromelysin-1</u>	<u>Gelatinase 72KD</u>
<u>Example No.</u>			
2	100000	802	1.43
3	385	2.75	0.01
4	302	1.73	0.014
5	554	18.7	0.047
6	800	6.8	0.01

The following abbreviations are used in the description of the preparation of Intermediates and in the Examples:

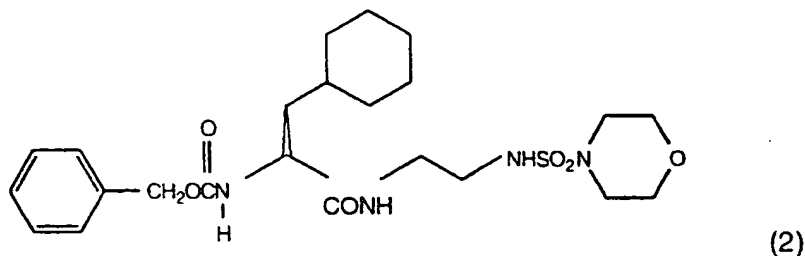
THF	tetrahydrofuran
EtOAc	ethyl acetate
DCCl	dicyclohexylcarbodiimide
MeOH	methanol
TFA	trifluoroacetic acid
NEt ₃	triethylamine
RT	room temperature
DMF	dimethylformamide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

INTERMEDIATE 1



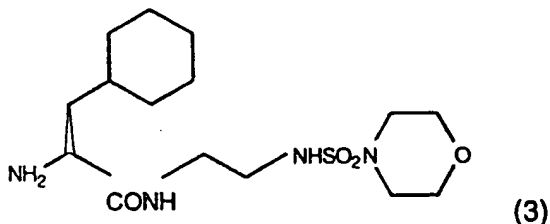
Morpholine sulphonyl chloride (10g; 53.9mmol) was added dropwise to ethylene diamine (200ml) and stirred at RT for 3 hours. Excess ethylene diamine was evaporated under reduced pressure, the residue was taken up in 1N HCl and the solvent was removed. The pale brown solid was extracted with MeOH and the insoluble precipitate of ethylene diamine dihydrochloride was filtered off. The filtrate was evaporated to give the desired sulphonyl urea (1) as a pale brown solid (9.5g).

¹Hnmr (D₂O) δ: 3.8 (4H, t); 3.45 (2H, t); 3.25 (4H, t); 3.15 (2H, t).

INTERMEDIATE 2

To a solution in dry DMF (50cm³) of N-CBZ-cyclohexylalanine (3.05g, 10mmol) was added N-methylmorpholine (2.31cm³, 21mmol), Intermediate 1 (2.35g, 9.57mmol), 1-hydroxybenzotriazole (20cm³ of 0.5N solution in DMF, 10mmol) and EDC (1.97g, 10mmol). The reaction mixture was stirred at room temperature for 18 hours then partitioned between diethyl ether and aqueous sodium carbonate solution. The organic layer was separated and washed with aqueous citric acid solution followed by water. The organic layer was separated, dried (MgSO₄) and evaporated. The residue was chromatographed on silica, eluting with 3% MeOH in CH₂Cl₂, to give the product (2) as a white solid (3.7g).

¹Hnmr (CDCl₃) δ: 7.2-7.4 (6H, m); 5.9 (2H, m); 5.1 (2H, dd); 4.2 (1H, dd); 3.7 (4H, t); 3.1-3.5 (8H, m); 0.8-1.8 (13H, m).

INTERMEDIATE 3

Intermediate 2 (2.99g, 5.8mmol) was dissolved in MeOH (100cm³) and 10% palladium on carbon catalyst was added. The reaction mixture was stirred at room temperature under an atmosphere of hydrogen for 3 hours. The catalyst was filtered off and the filtrate was evaporated to give the amine (3) as

a clear gum (2.1g).

¹Hnmr (CDCl₃) δ: 8.3 (1H, br s); 6.9-7.6 (2H, m); 4.2 (1H, t); 3.6-3.9 (6H, m); 3.1-3.4 (6H, m); 0.9-1.9 (15H, m).

INTERMEDIATE 4

2-(R)-[3-(4-methylphenyl)propyl]succinic acid-4-t-butyl monoester

- (a) (S)-3[1-oxo-5-(4-methylphenyl)pentyl]-4-(phenylmethyl)-2-oxazolidinone (1)

BuLi (1.6M solution in hexanes, 4.4mmol, 2.75 ml, 1.2 equiv.) was added dropwise to a solution of (S)-4-(phenylmethyl)-2-oxazolidinone (3.64mmol, 0.64g) in THF (15ml) at -78°C, under N₂ atmosphere. The orange solution was stirred for 30 mins at -78°C and then a solution of p-toylvalerylchloride (4.06mmol, 0.86g) in THF (5ml) was added dropwise. The reaction mixture was stirred at -78°C for 2 hrs before quenching at -78°C with a mixture of brine and 10% aqueous HCl (1:1, 20 ml). On warming to ambient temperature the reaction mixture was partitioned between EtOAc and water. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were washed once with brine, once with sodium bicarbonate solution and dried over MgSO₄. The solvent was removed under vacuum to give a brown oil which was purified on silica gel (Merck 9385) eluting with 20% EtOAc/hexane to give the compound as a slightly yellow oil (0.65g, 51%).

¹Hnmr (CDCl₃) δ: 1.63 (m, 4H); 2.31 (s, 3H); 2.62 (m, 2H); 2.75 (dd, 1H); 2.89-2.98 (m, 2H); 3.26 (dd, 1H); 4.12-4.18 (m, 2H); 4.61-4.67 (m, 1H); 7.17-7.36 (m, 9H).

- b) 3-[1-oxo-2(R)(t-butylacetyl)-5-(4-methylphenyl)pentyl]-4-(S)-phenylmethyl-2-oxazolidinone (2)

A solution of the oxazolidinone (1) (0.65g, 1.85mmol) in THF (10ml) was added to a solution of sodium bis(trimethylsilyl)azide (1M Solution in THF, 2.6mmol, 2.6ml, 1.4 equiv.) in THF (10ml) at -78°C under nitrogen. The reaction mixture was stirred at this temperature for 1 hr and then t-butylbromoacetate (5.6mmol, 1.08g, 0.90ml, 3 equiv.) was added dropwise. The reaction was allowed to warm to -20°C over 4 hours. The reaction was quenched at -78°C with a mixture of brine and 10% HCl (1:1, 20ml). The mixture was partitioned between EtOAc and water. The aqueous layer was separated and extracted twice with EtOAc. The combined EtOAc layers were washed once with brine and once with NaHCO₃ solution and dried over MgSO₄. The solvent was removed to give a yellow oil, which was purified on silica gel (Merck 9385) eluting with 20% EtOAc/hexane to give the compound (2) (0.57, 66%).

¹Hnmr (CDCl₃) δ: 1.42 (s, 9H); 1.57-1.62 (m, 2H); 2.30 (s, 3H); 2.41-2.85 (m, 5H); 3.33 (dd, 1H); 4.10-4.25 (m, 1H); 7.01-7.09 (m, 4H); 7.22-7.37 (m, 5H).

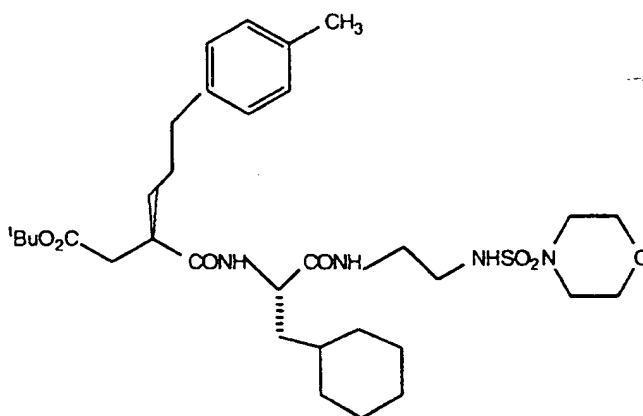
(c) 2-(R)-[3-(4-methylphenyl)propyl]succinic acid-4-t-butyl monoester (3)

A solution of the oxazolidinone (2) (0.57g, 1.23 mmol) in THF/water (4:1, 25ml) was cooled in an ice bath and treated with hydrogen peroxide solution (27.5 wt%, 4.9mmol, 0.56ml, 4 equiv). The mixture was stirred for a few minutes then a solution of lithium hydroxide monohydrate (1.23mmol, 52mg, 1.0 equiv.) in water (5ml) was added dropwise. The reaction was stirred for 90 mins then treated with a 10% aqueous solution of sodium sulphite (5ml). The reaction mixture was adjusted to pH 12-13 with 1M NaOH and then partitioned between dichloromethane and water. The aqueous layer was separated and acidified with 10% HCl. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed once with brine, once with NaHCO₃ solution and dried over MgSO₄ and the solvent removed to give the compound (3) as a yellowish oil (0.18g, 48%), which was used without further purification.

$^1\text{Hnmr}$ (CDCl_3) δ : 1.43 (s, 9H); 1.51-1.79 (m, 4H); 2.32 (2, 3H); 2.37 (dd, 1H); 2.82 (m, 1H); 7.03-7.12 (m, 4H).

EXAMPLE 1

{4-t-butoxy-2(R)-[3-(4-methylphenyl)propyl]succinyl}-L- β -cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl]amide



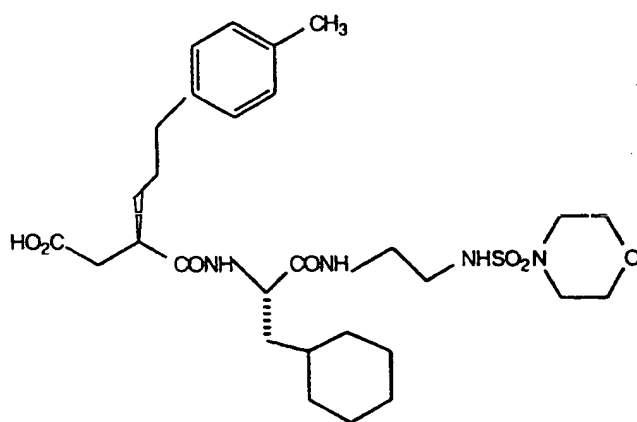
(1)

A solution of Intermediate 4 (0.2g) in THF (10ml) was treated with N-methyl morpholine (0.62mmol, 62.2mg, 67.7 μ l) and cooled to -20°C under N_2 . The mixture was then treated with ethyl chloroformate (0.59mmol, 64.1mg, 56.5 μ l) and stirred at -20°C for 1 hour during which time a white precipitate formed. After this time a solution of Intermediate 3 (150mg) in THF (5ml) was added dropwise and the reaction allowed to warm to ambient temperature overnight. The reaction was partitioned between EtOAc and water. The aqueous layer was separated and extracted twice with EtOAc. The combined EtOAc layers were washed once with 10% HCl, once with NaHCO_3 and once with brine, dried over MgSO_4 and the solvent removed under vacuum to give an oil which was purified on silica gel (Merck 9385) eluting with 1% MeOH/ CH_2Cl_2 to give 0.16g of the title compound as a slightly yellow oil.

$^1\text{Hnmr}$ (CDCl_3) δ : 7.05 (4H, 2d); 6.25 (1H, br d); 5.55 (1H, Br t); 4.30 (1H, m); 3.75 (4H, t); 3.1-3.5 (8H, m); 2.4-2.7 (5H, m); 2.3 (3H, s); 0.8-1.8 (26H, m).

EXAMPLE 2

{4-Hydroxy-2-(R)-[3-(4-methylphenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl] amide



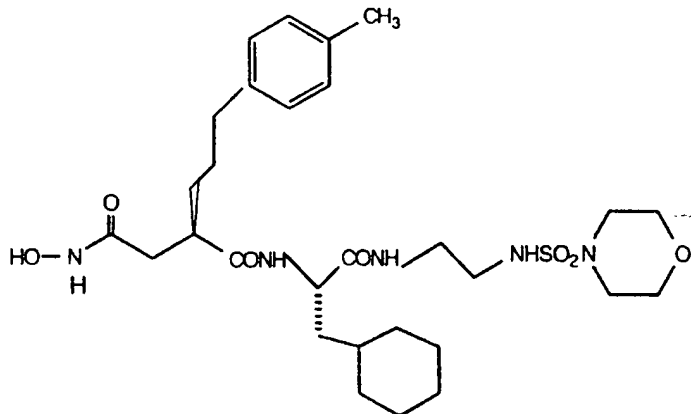
(2)

The t-butylester of Example 1 (0.2g) was treated with water (0.5ml) and TFA (2.5ml) and allowed to stand overnight (18h). The volatiles were removed under vacuum to give an oil which solidified on standing. Trituration with diisopropyl ether gave the title compound (2) as powdery solid.

¹Hnmr (CDCl₃) δ: 7.5 (1H, t); 7.0.5 (4H, d); 4.4 (1H, m); 3.75 (4H, t); 3.1-3.6 (8H, m); 2.5-2.8 (5H, m); 2.3 (3H, s); 0.8-1.8 (17H, m).

EXAMPLE 3

{4-(N-Hydroxyamino)-2(R)-[3-(4-methylphenyl)propyl)succinyl]-L-β-cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl] amide



(3)

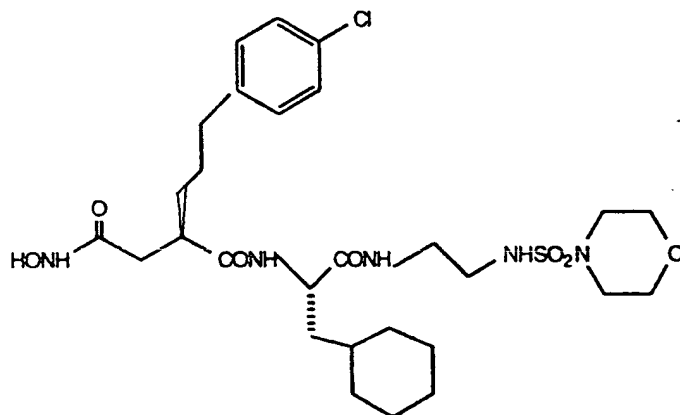
The compound of Example (2) (405mg, 0.68mmol) was dissolved in dry THF (5cm³) and cooled to -20°C. N-methylmorpholine (89μl, 0.80mmol) and ethyl chloroformate (72μl, 0.75mmol) were added and the reaction mixture was stirred at -16°C for 1 hour. O-trimethylsilylhydroxylamine (360μl, 3.4mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and aqueous citric acid. The organic layer was separated, dried (MgSO₄) and evaporated. The desired hydroxamic acid (3) was purified by reverse phase HPLC (Dyanax C18 column), eluting at 15.3 minutes under a 40 → 60% acetonitrile in water gradient. Yield: 220mg.

¹Hnmr (CD₃OD) δ: 7.05 (4H, s); 4.25 (1H, dd); 3.70 (4H, t); 3.1-3.4 (8H, m); 2.5-2.8 (3H, m); 2.40 (1H, dd); 2.30 (3H, s); 2.25 (1H, dd); 0.8-1.8 (17H, m).

The following compounds were made following the general teaching Example 3 using the analogous starting materials.

EXAMPLE 4

{4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-
L-β-cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl]
amide

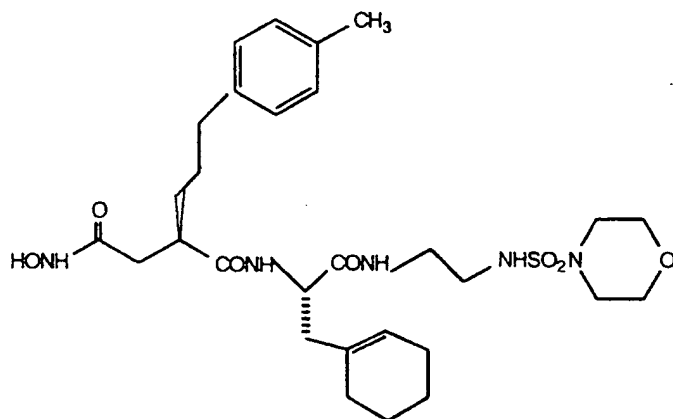


(4)

¹Hnmr (CD₃OD) δ: 8.20 (1H, m); 7.25 (2H, d); 7.16 (2H, d); 4.29 (1H, m); 3.70 (4H, m); 3.32 (2H, m); 3.11 (6H, m); 2.72 (1H, m); 2.60 (2H, m); 2.40 (1H, dd); 2.20 (1H, dd); 1.9-0.8 (17H, m).

EXAMPLE 5

{4-(N-Hydroxyamino)-2(R)-[3-(4-methylphenylpropyl)succinyl]-L-
β-(1-cyclohexenylalanine)-N-[(2-morpholinesulphonylamino)
ethyl]amide

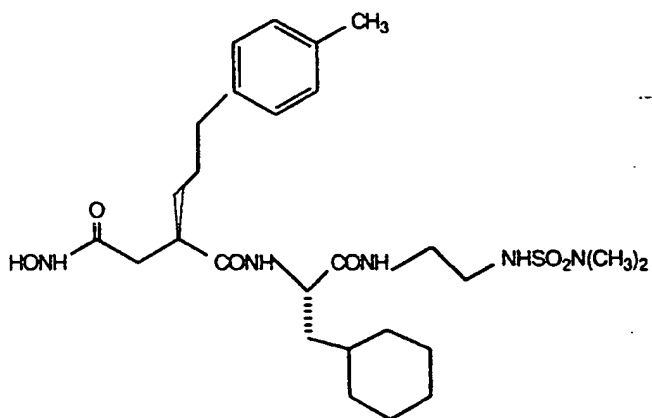


(5)

¹Hnmr (CD₃OD) δ: 7.05 (4H, m); 5.50 (1H, m); 4.35 (1H, m); 3.70 (4H, t); 3.30 (2H, m); 3.15 (6H, m); 2.75-2.20 (8H, m); 2.0-1.35 (14H, m).

EXAMPLE 6

{4-(N-Hydroxyamine)-2(R)-[3-(4-methylphenyl)propyl]succinyl}-
L-β-cyclohexylalanine-N-[(2-dimethylsulphonylamino)propyl]
amide

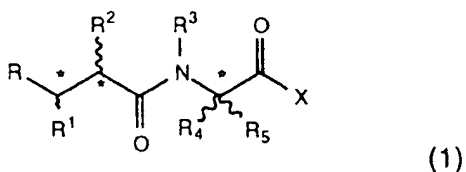


(6)

¹Hnmr (CD₃OD) δ: 7.05 (4H, m); 4.30 (1H, m); 3.30 (2H, m); 3.10 (2H, t); 2.7-2.8 (7H, m); 2.60 (2H, m); 2.40 (1H, dd); 2.25 (3H, s); 2.20 (1H, dd); 1.8-0.9 (17H, m).

CLAIMS

1. A compound of formula (1):



wherein R represents a - CONHOH, carboxyl (-CO₂H), esterified carboxyl or -P(O)(X¹R⁸)X²R⁹ group, where X¹ and X², which may be the same or different is each an oxygen or a sulphur atom, and R⁸ and R⁹, which may be the same or different each represents a hydrogen atom or an optionally substituted alkyl, aryl or aralkyl group;

R¹ represents a hydrogen atom or an optionally substituted alkyl, alkenyl, aryl, aralkyl, heteraralkyl or heteroarylthiolalkyl group;

R² represents an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkoxy, or aralkylthio group, or an amino (-NH₂), substituted amino, carboxyl (-CO₂H) or esterified carboxyl group;

R³ represents a hydrogen atom or an alkyl group;

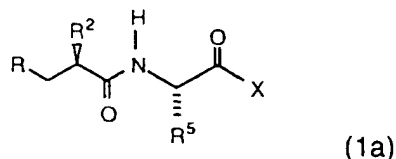
R⁴ represents a hydrogen atom or an alkyl group;

R⁵ represents an optionally substituted alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms or -NR⁷- groups, [where R⁷ is a hydrogen atom or a C₁₋₆ alkyl group] or a group -[Alk]_nR⁶ where Alk is an alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R⁷)- groups, n is zero or an integer, and R⁶ is an optionally substituted cycloalkyl or cycloalkenyl group;

X represents a group $-NR^{10}R^{11}$ where R^{10} is a hydrogen atom or an optionally substituted alkyl, alkanoyl, aryl, aroyl, aralkyl or aralkanoyl group, and R^{11} is a straight or branched alkylaminosulphonylamino group wherein the alkyl portion is optionally interrupted by one or more -O- or -S- atoms or $N(R^7)$ - or amino carbonyloxy groups;

and the salts, solvates and hydrates thereof;

2. A compound according to Claim 1 wherein R represents a -CONHOH group.
3. A compound according to Claims 1 and 2 wherein R^1 , R^3 and R^4 is each a hydrogen atom.
4. A compound according to any of Claims 1-3 where R^2 is an optionally substituted phenylpropyl group.
5. A compound according to any of Claims 1-4 wherein R^5 is a cyclohexyl C_{1-6} alkyl group.
6. A compound according to any of Claims 1-5 wherein R^5 is a cyclohexylmethyl group.
7. A compound according to any of the Claims 1-6 wherein X is a $Alk^1 N(R^7)SO_2NR^{12}R^{13}$ group, wherein Alk^1 is straight or branched C_{1-6} alkyl optionally interrupted by one or more -O- or -S- atoms or $N(R^7)$ - or aminocarbonyloxy groups, and R^{12} and R^{13} is each an optionally substituted C_{1-6} alkyl group or R^{12} and R^{13} together with the nitrogen atom to which they are attached is an optionally substituted C_{3-6} cyclic amino group.
8. A compound according to Claim 7 where Alk^1 is a C_{1-3} alkyl group.
9. A compound of formula (1a)



wherein R represents a -CONHOH, carboxyl (-CO₂H) or esterified carboxyl group;

R² represents an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkoxy or aralkylthio group, or an amino (-NH₂), substituted amino, carboxyl (-CO₂H) or esterified carboxyl group,

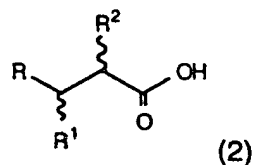
R⁵ represents an optionally substituted alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atom or -N(R⁷) groups, [where R⁷ is a hydrogen atom or a C₁₋₆ alkyl group] or a group -(Alk)_nR⁶ where Alk is an alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R⁷)- groups, n is zero or an integer and R⁶ is an optionally substituted cycloalkyl or cycloalkenyl group; X represents a group -NR¹⁰R¹¹ where R¹⁰ is a hydrogen atom or an optionally substituted alkyl, alkanoyl, aroyl, aralkyl or aralkanoyl group, and R¹¹ is a straight or branched alkyl-aminosulphonylamino group where the alkyl portion is optionally interrupted by one or more -O- or -S- atoms or N(R⁷) or amino-carbonyloxy group; and the salts, solvates and hydrates thereof.

10. {4-Hydroxy-2-(R)-[3-(4-methylphenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl]amide;
 {4-(N-Hydroxyamino)-2-(R)-[3-(4-methylphenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl]amide;
 {4-(N-Hydroxyamino)-2-(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl]amide;
 {4-N-Hydroxyamino-2-(R)-[3-(4-methylphenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-dimethylsulphonylamino)propyl]amide;

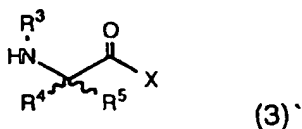
and the salts, solvates and hydrates thereof.

11. A pharmaceutical composition comprising a compound according to any one of Claims 1-12 and a pharmaceutically acceptable diluent, carrier or excipient.
12. A process for preparing a compound of formula (1) as defined in Claim 1, the process comprising:

a) coupling an acid of formula (2)

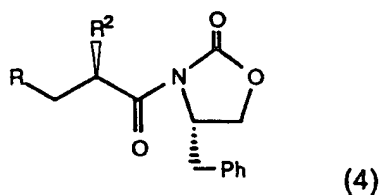


or an active and/or protected derivative thereof, with an amine of formula (3)



followed by removal of any protecting group.

b) oxidising an oxazolidinone of formula (4)



or c) interconverting a compound of formula (1) to another compound of formula (1).

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/01185

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D295/22; C07C307/06; A61K31/535; A61K31/095		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; C07C	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	WO,A,9 005 716 (BRITISH BIO-TECHNOLOGY) 31 May 1990 cited in the application see page 7 - page 9; claims 1,14 ---	1,2,11
A	WO,A,9 102 716 (BRITISH BIO-TECHNOLOGY) 7 March 1991 see page 7 - page 9; claims 1,14 -----	1,2,11
<p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
10 SEPTEMBER 1993	21.09.93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	RUSSELL F. ENGLISH	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9301185
SA 75172

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 10/09/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9005716	31-05-90	AU-A- 4746890	12-06-90
		EP-A- 0445206	11-09-91
		JP-T- 4503057	04-06-92

WO-A-9102716	07-03-91	AU-A- 6045490	03-04-91
		EP-A- 0489032	10-06-92
		JP-T- 5501864	08-04-93
